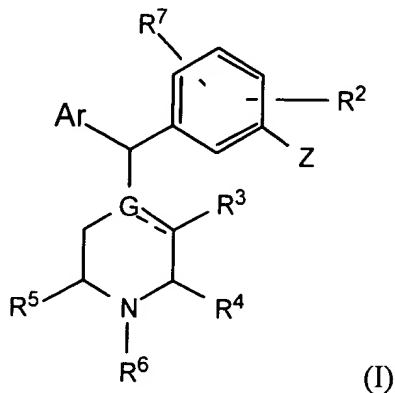


49. The pharmaceutical composition of claim 47, wherein the  $\delta$  receptor activating agent comprises a diarylmethylpiperazine compound.
50. The pharmaceutical composition of claim 47, wherein the  $\delta$  receptor activating agent comprises 3290W93.
51. The pharmaceutical composition of claim 47, wherein the  $\delta$  receptor activating agent comprises BW373U86.
52. The pharmaceutical composition of claim 47, wherein the  $\delta$  receptor activating agent comprises an agent selected from the group consisting of:

- I. diarylmethylpiperazine compounds;
- II. diarylmethylpiperidine compounds;
- III. deltorphin I; and
- III. deltorphin II.

53. The pharmaceutical composition of claim 47, wherein the  $\delta$  receptor activating agent comprises an agent selected from the group consisting of:

- I.  $\delta$  agonist compounds of the formula:



wherein:

Ar is a 5- or 6-member carbocyclic or heterocyclic aromatic ring with atoms selected from the group consisting of carbon, nitrogen, oxygen and sulfur, and having on a first carbon atom thereof a substituent Y and on a second ring carbon thereof a substituent  $R^1$ ;

Y is selected from the group consisting of:

hydrogen;

halogen;

C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl;

C<sub>1</sub>-C<sub>6</sub> haloalkyl;

C<sub>1</sub>-C<sub>6</sub> alkoxy;

C<sub>3</sub>-C<sub>6</sub> cycloalkoxy;

sulfides of the formula  $SR^8$  where  $R^8$  is C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, arylalkyl having a C<sub>5</sub>-C<sub>10</sub> aryl moiety and an C<sub>1</sub>-C<sub>6</sub> alkyl moiety, or C<sub>5</sub>-C<sub>10</sub> aryl;

sulfoxides of the formula  $SOR^8$  where  $R^8$  is the same as above;

sulfones of the formula  $SO_2R^8$  where  $R^8$  is the same as above;

nitrile;

C<sub>1</sub>-C<sub>6</sub> acyl;

alkoxycarbonylamino (carbamoyl) of the formula  $\text{NHCO}_2\text{R}^8$  where  $\text{R}^8$  is the same as above;

carboxylic acid, or an ester, amide, or salt thereof;

aminomethyl of the formula  $\text{CH}_2\text{NR}^9\text{R}^{10}$  where  $\text{R}^9$  and  $\text{R}^{10}$  may be the same or different, and may be hydrogen,  $\text{C}_1$ - $\text{C}_6$  alkyl,  $\text{C}_2$ - $\text{C}_6$  alkenyl,  $\text{C}_2$ - $\text{C}_6$  alkynyl,  $\text{C}_2$ - $\text{C}_6$  hydroxyalkyl,  $\text{C}_2$ - $\text{C}_6$  methoxyalkyl,  $\text{C}_3$ - $\text{C}_6$  cycloalkyl, or  $\text{C}_5$ - $\text{C}_{10}$  aryl, or  $\text{R}^9$  and  $\text{R}^{10}$  together may form a ring of 5 or 6 atoms, the ring atoms selected from the group consisting of N and C;

carboxamides of the formula  $\text{CONR}^9\text{R}^{10}$  where  $\text{R}^9$  and  $\text{R}^{10}$  are the same as above, or  $\text{C}_2$ - $\text{C}_{30}$  peptide conjugates thereof; and

sulfonamides of the formula  $\text{SO}_2\text{NR}^9\text{R}^{10}$  where  $\text{R}^9$  and  $\text{R}^{10}$  are the same as above;

Z is selected from the group consisting of:

hydroxyl, and esters thereof;

hydroxymethyl, and esters thereof; and

amino, and carboxamides and sulfonamides thereof;

G is carbon or nitrogen;

$\text{R}^1$  is hydrogen, halogen, or  $\text{C}_1$ - $\text{C}_4$  alkyl,  $\text{C}_2$ - $\text{C}_4$  alkenyl,  $\text{C}_1$ - $\text{C}_4$  alkynyl;

$\text{R}^2$  is hydrogen, halogen, or  $\text{C}_1$ - $\text{C}_4$  alkyl,  $\text{C}_2$ - $\text{C}_4$  alkenyl,  $\text{C}_1$ - $\text{C}_4$  alkynyl;

$R^3$ ,  $R^4$  and  $R^5$  may be the same or different, and are independently selected from hydrogen and methyl, and wherein at least one of  $R^3$ ,  $R^4$  or  $R^5$  is not hydrogen, subject to the proviso that the total number of methyl groups does not exceed two, or any two of  $R^3$ ,  $R^4$  and  $R^5$  together may form a bridge of 1 to 3 carbon atoms;

$R^6$  is selected from the group consisting of:

hydrogen;

C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl;

C<sub>3</sub>-C<sub>6</sub> cycloalkyl;

arylalkyl having C<sub>5</sub>-C<sub>10</sub> aryl and C<sub>1</sub>-C<sub>6</sub> alkyl moieties;

alkoxyalkyl having C<sub>1</sub>-C<sub>4</sub> alkoxy and C<sub>1</sub>-C<sub>4</sub> alkyl moieties;

C<sub>2</sub>-C<sub>4</sub> cyanoalkyl;

C<sub>2</sub>-C<sub>4</sub> hydroxyalkyl;

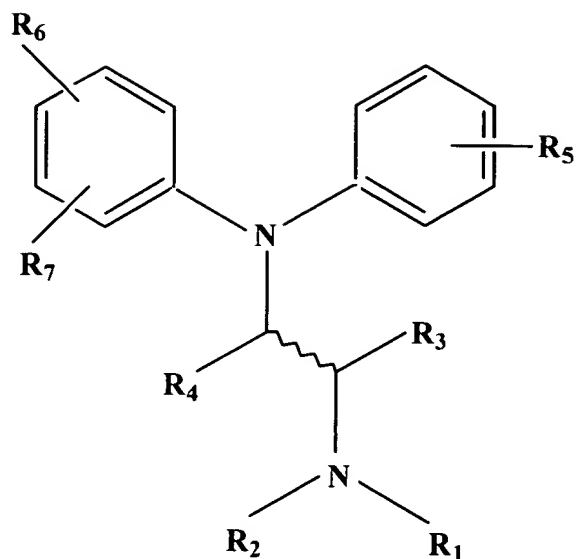
aminocarbonylalkyl having a C<sub>1</sub>-C<sub>4</sub> alkyl moiety; and

$R^{12}COR^{13}$ , where  $R^{12}$  is C<sub>1</sub>-C<sub>4</sub> alkylene, and  $R^{13}$  is C<sub>1</sub>-C<sub>4</sub> alkyl or C<sub>1</sub>-C<sub>4</sub> alkoxy; and

$R^7$  is hydrogen or fluorine,

or a pharmaceutically acceptable ester or salt thereof;

II. delta agonist compounds of the formula:



in which,

R<sub>1</sub> and R<sub>2</sub>, which can be the same or different, are each hydrogen, linear or branched C<sub>1-6</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkenyl, C<sub>4-6</sub> cycloalkylalkyl, C<sub>3-6</sub> alkenyl, C<sub>3-5</sub> alkynyl, aryl, aralkyl or furan-2 or 3-yl alkyl or may form together a C<sub>3-7</sub> alkyl ring which may be interrupted by oxygen.

R<sub>3</sub> and R<sub>4</sub>, which can be the same or different, are each hydrogen, linear or branched C<sub>1-6</sub> alkyl, or R<sub>4</sub> is oxygen forming with the carbon atom to which is attached a C=O group;

R<sub>5</sub> is hydrogen, hydroxy, C<sub>1-3</sub> alkoxy, thiol or alkylthio;

R<sub>6</sub> is phenyl, halogen, NH<sub>2</sub> or a para or meta -C(Z)-R<sub>8</sub> group, in which Z is oxygen or sulphur;

R<sub>8</sub> is C<sub>1-8</sub>-alkyl, C<sub>1-8</sub>-alkoxy or NR<sub>9</sub>R<sub>10</sub>, wherein R<sub>9</sub> and R<sub>10</sub>, which may be the same or different, are hydrogen, straight or branched C<sub>1-6</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>4-6</sub> cycloalkylalkyl, C<sub>3-6</sub> alkenyl, aryl or aralkyl,

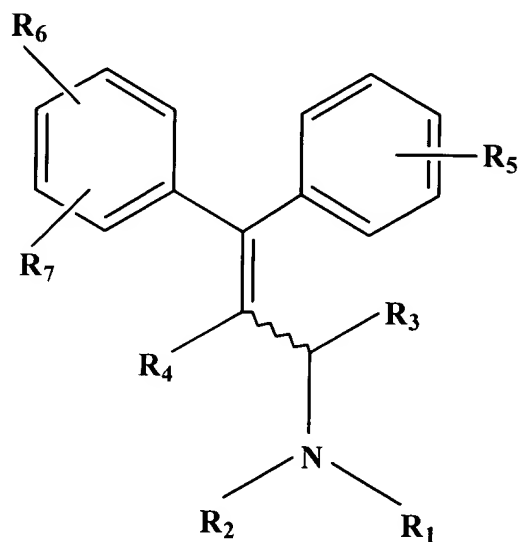
or R<sub>6</sub> is a para or meta -N-C(Z)-R<sub>12</sub> group



in which  $R_{11}$  and  $R_{12}$  which may be the same or different are hydrogen, straight or branched  $C_{1-6}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{4-6}$  cycloalkylalkyl,  $C_{3-6}$  alkenyl, aryl, aralkyl or an optionally substituted heterocyclic ring, and Z is as defined above; and,

$R_7$  is hydrogen, straight or branched  $C_{1-8}$  alkyl or halogen; and

III. delta agonist compounds of the formula:



in which,

$R_1$  and  $R_2$ , which can be the same or different, are each hydrogen, linear or branched  $C_{1-6}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{3-7}$  cycloalkenyl,  $C_{4-6}$  cycloalkylalkyl,  $C_{3-6}$  alkenyl,  $C_{3-5}$  alkynyl, aryl, aralkyl or furan-2 or 3-yl alkyl or may form together a  $C_{3-7}$  alkyl ring which may be interrupted by oxygen.

$R_3$  and  $R_4$ , which can be the same or different, are each hydrogen, linear or branched  $C_{1-6}$  alkyl;

$R_5$  is hydroxy,  $C_{1-6}$  alkoxy, thiol or alkylthio;

$R_6$  is a  $-C(Z)-R_8$  group, in which Z is oxygen or sulphur,  $R_8$  is  $C_{1-8}$ -alkyl,  $C_{1-8}$ -alkoxy or  $NR_9R_{10}$ , wherein  $R_9$  and  $R_{10}$ , which may be the same or different, are hydrogen, straight or branched  $C_{1-6}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{4-6}$  cycloalkylalkyl,  $C_{3-6}$  alkenyl, aryl or aralkyl,

or R<sub>6</sub> is a  $\begin{array}{c} \text{R}_{11} \\ | \\ -\text{N}-\text{C}(\text{Z})-\text{R}_{12} \end{array}$  group

in which R<sub>11</sub> and R<sub>12</sub> have the same meaning as R<sub>9</sub> and R<sub>10</sub> or together form an optionally substituted heterocyclic ring and Z is as defined above, and R<sub>7</sub> is hydrogen, straight or branched C<sub>1-8</sub> alkyl or halogen.

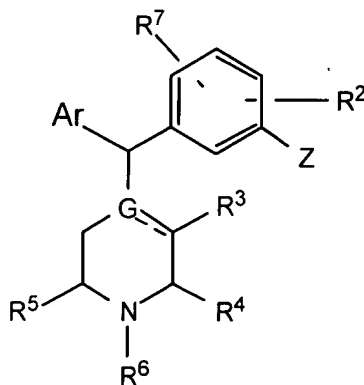
54. The pharmaceutical composition of claim 47, in a form suitable for injectable or spinal administration.

55. A pharmaceutical composition comprising:

(a) an effective amount of a bioactive compound mediating respiratory depression; and

(b) an effective amount of a non-polypeptide  $\delta$  receptor activating agent effective for combating said respiratory depression.

56. A pharmaceutical composition comprising an effective amount of a bioactive composition mediating respiratory depression, and an effective amount of a compound for reducing, treating or preventing respiratory depression, of the formula:



(I)

wherein:

Ar is a 5- or 6-member carbocyclic or heterocyclic aromatic ring with atoms selected from the group consisting of carbon, nitrogen, oxygen and sulfur, and having on a first carbon atom thereof a substituent Y and on a second ring carbon thereof a substituent  $R^1$ ;

Y is selected from the group consisting of:

hydrogen;

halogen;

C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl;

C<sub>1</sub>-C<sub>6</sub> haloalkyl;

C<sub>1</sub>-C<sub>6</sub> alkoxy;

C<sub>3</sub>-C<sub>6</sub> cycloalkoxy;

sulfides of the formula  $SR^8$  where  $R^8$  is C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, arylalkyl having a C<sub>5</sub>-C<sub>10</sub> aryl moiety and an C<sub>1</sub>-C<sub>6</sub> alkyl moiety, or C<sub>5</sub>-C<sub>10</sub> aryl;

sulfoxides of the formula  $SOR^8$  where  $R^8$  is the same as above;

sulfones of the formula  $SO_2R^8$  where  $R^8$  is the same as above;

nitrile;

C<sub>1</sub>-C<sub>6</sub> acyl;

alkoxycarbonylamino (carbamoyl) of the formula  $NHCO_2R^8$  where  $R^8$  is the same as above;

carboxylic acid, or an ester, amide, or salt thereof;

aminomethyl of the formula  $\text{CH}_2\text{NR}^9\text{R}^{10}$  where  $\text{R}^9$  and  $\text{R}^{10}$  may be the same or different, and may be hydrogen,  $\text{C}_1\text{-C}_6$  alkyl,  $\text{C}_2\text{-C}_6$  alkenyl,  $\text{C}_2\text{-C}_6$  alkynyl,  $\text{C}_2\text{-C}_6$  hydroxyalkyl,  $\text{C}_2\text{-C}_6$  methoxyalkyl,  $\text{C}_3\text{-C}_6$  cycloalkyl, or  $\text{C}_5\text{-C}_{10}$  aryl, or  $\text{R}^9$  and  $\text{R}^{10}$  together may form a ring of 5 or 6 atoms, the ring atoms selected from the group consisting of N and C;

carboxamides of the formula  $\text{CONR}^9\text{R}^{10}$  where  $\text{R}^9$  and  $\text{R}^{10}$  are the same as above, or  $\text{C}_2\text{-C}_{30}$  peptide conjugates thereof; and

sulfonamides of the formula  $\text{SO}_2\text{NR}^9\text{R}^{10}$  where  $\text{R}^9$  and  $\text{R}^{10}$  are the same as above;

Z is selected from the group consisting of:

hydroxyl, and esters thereof;

hydroxymethyl, and esters thereof; and

amino, and carboxamides and sulfonamides thereof;

G is carbon or nitrogen;

$\text{R}^1$  is hydrogen, halogen, or  $\text{C}_1\text{-C}_4$  alkyl,  $\text{C}_2\text{-C}_4$  alkenyl,  $\text{C}_1\text{-C}_4$  alkynyl;

$\text{R}^2$  is hydrogen, halogen, or  $\text{C}_1\text{-C}_4$  alkyl,  $\text{C}_2\text{-C}_4$  alkenyl,  $\text{C}_1\text{-C}_4$  alkynyl;

$\text{R}^3$ ,  $\text{R}^4$  and  $\text{R}^5$  may be the same or different, and are independently selected from hydrogen and methyl, and wherein at least one of  $\text{R}^3$ ,  $\text{R}^4$  or  $\text{R}^5$  is not hydrogen, subject to the proviso that the total number of methyl groups does not exceed two, or any two of  $\text{R}^3$ ,  $\text{R}^4$  and  $\text{R}^5$  together may form a bridge of 1 to 3 carbon atoms;

$R^6$  is selected from the group consisting of:

hydrogen;

C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl;

C<sub>3</sub>-C<sub>6</sub> cycloalkyl;

arylalkyl having C<sub>5</sub>-C<sub>10</sub> aryl and C<sub>1</sub>-C<sub>6</sub> alkyl moieties;

alkoxyalkyl having C<sub>1</sub>-C<sub>4</sub> alkoxy and C<sub>1</sub>-C<sub>4</sub> alkyl moieties;

C<sub>2</sub>-C<sub>4</sub> cyanoalkyl;

C<sub>2</sub>-C<sub>4</sub> hydroxyalkyl;

aminocarbonylalkyl having a C<sub>1</sub>-C<sub>4</sub> alkyl moiety; and

$R^{12}COR^{13}$ , where  $R^{12}$  is C<sub>1</sub>-C<sub>4</sub> alkylene, and  $R^{13}$  is C<sub>1</sub>-C<sub>4</sub> alkyl or C<sub>1</sub>-C<sub>4</sub> alkoxy; and

$R^7$  is hydrogen or fluorine,

or a pharmaceutically acceptable ester or salt thereof.

57. The pharmaceutical composition according to claim 56, wherein Ar is a 6-member carbocyclic aromatic (benzene) ring and  $R^1$  is hydrogen.

58. The pharmaceutical composition according to claim 56, wherein Y is a carboxamide of the formula  $CONR^9R^{10}$ .

59. The pharmaceutical composition according to claim 56, wherein  $R^9$  and  $R^{10}$  together form a ring of five or six atoms, thereby forming a pyrrolidinyl or piperidino ring.

60. The pharmaceutical composition according to claim 56, wherein  $R^9$  and  $R^{10}$  are the same or different and are each independently selected from hydrogen,  $C_1$  alkyl and  $C_2$  alkyl.

61. The pharmaceutical composition according to claim 56, wherein Y is hydrogen.

62. The pharmaceutical composition according to claim 56, wherein Y is a sulfone of the formula  $SO_2R^8$  and  $R^8$  is  $C_1$ - $C_6$  alkyl.

63. The pharmaceutical composition according to claim 56, wherein G is N,  $R^7$  and  $R^2$  are each hydrogen, and Z is hydroxyl.

64. The pharmaceutical composition according to claim 56, wherein  $R^6$  is selected from the group consisting of hydrogen,  $C_1$ - $C_6$  alkyl,  $C_2$ - $C_6$  alkenyl and  $C_2$ - $C_6$  alkynyl.

65. The pharmaceutical composition according to claim 56, wherein  $R^3$ ,  $R^4$  and  $R^5$  are hydrogen or methyl, where the total number of methyl groups is one or two.

66. The pharmaceutical composition according to claim 56, wherein  $R^3$  and  $R^5$  are both methyl, and  $R^4$  is hydrogen.

67. The pharmaceutical composition according to claim 47, wherein the  $\delta$  receptor activating agent comprises a compound selected from the group consisting of:

(-)-4-(( $\alpha R$ )- $\alpha$ -((2R,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethylbenzamide;

(-)-4-(( $\alpha R$ )- $\alpha$ -((2R,5R)-2,5-dimethyl-4-propyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethylbenzamide;

4-(( $\alpha R$ )- $\alpha$ -(2S,5S)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)benzamide;

(±)-3-((αR\*)-α-((2S\*,5R\*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)benzamide;

N,N-diethyl-4-((αR)-3-hydroxy-α-((2R,5R)-2,5-dimethyl-1-piperazinyl)benzyl)benzamide;

4-((αR)-α-((2S,5S)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-ethyl-N-methylbenzamide;

3-((αR)-α-((2S,5S)-4-allyl-2,5-dimethyl-1-piperazinyl)benzyl)phenol;

(±)-N,N-diethyl-4-((αR\*)-3-hydroxy-α-((2R\*,5S\*)-2,4,5-trimethyl-1-piperazinyl)benzyl)benzamide;

(+)-4-((αS)-α-((2S,5S)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethylbenzamide;

3-((αR)-4-(piperidinocarbonyl)-α-((2S,5S)-2,4,5-trimethyl-1-piperazinyl)benzyl)phenol;

3-((αR)-4-(1-pyrrolidinylcarbonyl)-α-((2S,5S)-2,4,5-trimethyl-1-piperazinyl)benzyl)phenol;

(±)-3-((αR\*)-α-((2R\*,5S\*)-4-allyl-2,5-dimethyl-1-piperazinyl)-4-(methylsulfonyl)benzyl)phenol;

(±)-4-((αR\*)-α-((2R\*,5S\*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-dimethylbenzenesulfonamide;

(+)-4-((αR)-α-((2R,5S)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-dimethylbenzenesulfonamide; or

(-)-4-((αR)-α-((2R,5S)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-dimethylbenzenesulfonamide;

(±)-3-((αR\*)-α-((2S\*,5R\*)-4-allyl-2,5-dimethyl-1-piperazinyl)benzyl)phenol;

(±)-4-((αR\*)-α-((2S\*,5R\*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)benzamide;

(±)-4-((αR\*)-α-((2R\*,5S\*)-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethylbenzamide;

(±)-cis-4-(α-(4-allyl-3,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethylbenzamide;

cis-4-(α-(3,5-dimethyl-4-(methylallyl)-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethylbenzamide;

and pharmaceutically acceptable salts thereof.

68. The pharmaceutical composition of claim 47, wherein the δ receptor activating agent comprises

(-)-4-((αR)-α-((2R,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethylbenzamide or a pharmaceutically acceptable salt thereof.

69. The pharmaceutical composition of claim 47, wherein the bioactive compound comprises an opiate compound.

70. The pharmaceutical composition of claim 47, wherein the bioactive compound comprises an opiate analgesic compound.

71. The pharmaceutical composition of claim 47, wherein the bioactive compound comprises a μ opiate compound.

72. The pharmaceutical composition of claim 47, wherein the bioactive compound comprises at least one active ingredient selected from the group consisting of alcohol, aldesleukin, alfentanil, bremazocine, buprenorphine, butorphanol, chlorpromazine, clozapine, codeine, dantrolene, diazepam, dihydrocodeine, etorphine, fentanyl, flurazepam, heroin, hydrocodone, hydromorphone, ketamine, larazepam, levallorphen, levorphanol, meperidine, methadone, methohexital, mitomycin, morphine, nalbuphine, opium, oxazepam, oxycodone, oxymorphone, pentazocine, phenobarbital, porfimer, propoxyphene, resperidone, sufentanil, temazepam, thiopental, thiorzadine, tramadol, trimethaphan, and zolpidem.

73. A pharmaceutical composition comprising: